NAFLD
Non-alcoholic fatty liver disease

Using the current knowledge to optimally manage the disease at various stages

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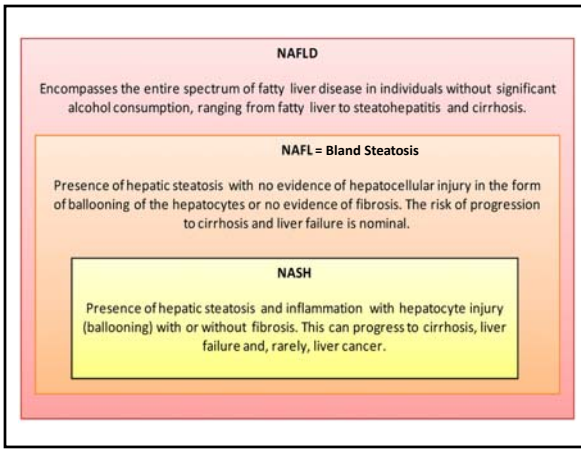
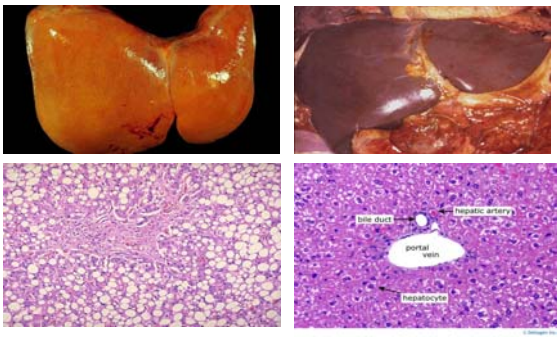
NAFLD-Introduction

- NAFLD was coined in 1980 by Dr. Ludwig, Mayo Clinic
- 30-35% population of US have NAFLD (90+ million!)
- Most common cause for elevated transaminases
- Projected to be #1 cause for liver txp in US and World by 2020-2025
- Liver manifestation of Obesity/ Insulin resistance

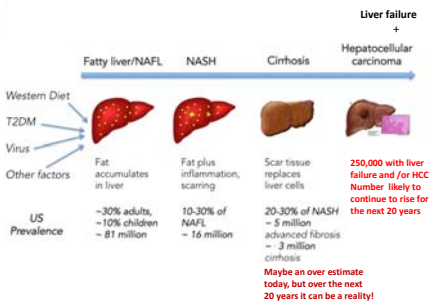


Fatty liver Normal liver



NAFLD –Stages and Numbers

Estimates of US population at various stages of NAFLD



Rosana Kapeller, CSO of Nimbus Therapeutics
From Crawl to Sprint: The Race to Treat NASH May,2015 *LifeSciVC*

Extra Hepatic Diseases Associated with NAFLD

- Insulin Resistance/Impaired glucose tolerance/Type-2 DM
- Dyslipidemia, Gout, Hypertension,
- Cardiovascular / Cerebrovascular Disease/ Heart Failure
- Osteoarthritis/ Osteopenia
- Obstructive Sleep Apnea
- Extra hepatic Malignancies- Esophagus/Pancreas/Breast/Colon/Endometrium
- Chronic renal Insufficiency, Kidney stones, BPH, LUTS
- Alzheimer's disease

While all these conditions appear to be also associated with Obesity and T2DM, the presence of NAFLD and especially NASH appears to independently increase the incidence of most of them

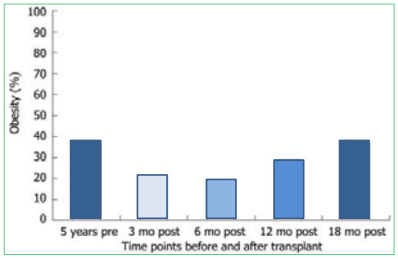
NAFLD and Liver Txp

- At UCLA, the largest liver transplant center in US nearly 25% of transplants in 2014 for NASH, up from 3% in 2002.
- In the United States right now, we do about 6000 liver transplants a year.
- That would be a much smaller fraction of those with liver failure if the epidemic is not controlled

Threat Grows From Liver Illness Tied to Obesity
By Anahad O'Connor NY Times June 13, 2014

NAFLD after Liver Transplantation

prevalence of obesity before and after liver transplant



Eric R Kallwitz- World J Gastroenterol. 2012 July 28; 18(28): 3627-3634

What are the causes of Morbidity and Mortality in patients with Fatty liver?

This knowledge would help in patient management by allowing us to design preventive and screening strategies for specific problems that are more prevalent than in those without NAFLD

The easy answer is that the patients with NAFLD have increased incidence of liver failure and liver cancer

However…..

Cause of Death in Patients with NAFLD

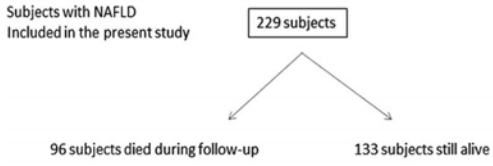
CAUSE OF DEATH	Stage of Liver Fibrosis					
	1	2	3	4	0	TOTAL
Cirrhosis and/or Liver cancer	1		3	5		9
Extrahepatic cancer	2	6	1	2	1	12
Cardiovascular	4	6	3	1	1	15
Diabetes		2			1	3
Other	3			1	1	3

Study to determine the frequency of NAFLD in a cohort of subjects (Karolinska Institute Stockholm, Sweden)) who underwent liver biopsy from 1980 to 1984 because of elevated liver enzymes, and to assess mortality among subjects with NAFLD in comparison with the general Swedish population- mean follow up of over 20 yrs.

Modified from Cecilia Söderberg et al
Hepatology-Volume 51, Issue 2, pages 595–602, February 2010

Fibrosis Stage Is the Strongest Predictor of Mortality in NAFLD After 6-33 Years of Follow up

Another recent Swedish study – Some overlap of patients from the first study



Mattias Ekstedt et al HEPATOLOGY 2015;61:1547-1554

Fibrosis Stage Is the Strongest Predictor of Mortality in NAFLD After 6-33 Years of Follow up

Cause of Death	Patients (n = 96)
Cardiovascular disease	41 (43%)
Non-Liver malignancy	22 (23%)
Hepatocellular carcinoma/ Cirrhosis	9 (9%)
Infection	5 (5%)
Diabetes complications	3 (3%)
Respiratory	3 (3%)
Other	7 (7%)
Missing	6 (6%)

Cause of Death in NAFLD Patients

Mattias Ekstedt et al HEPATOLOGY 2015;61:1547-1554

Fibrosis Stage Is the Strongest Predictor of Mortality in NAFLD After 6-33 Years of Follow up

Subgroups Compared With the Reference Population [HR (95% CI)]

Cause of Death	Entire Cohort (n = 229)	P	F3-4 (n=16)	P
Overall mortality	1.29 (1.04-1.59)	0.020	3.28 (2.27-4.76)	<0.001
Cardiovascular disease	1.55 (1.11-2.15)	0.01	4.36 (2.29-8.29)	<0.001
Hepatocellular carcinoma	6.55 (2.14-20.0)	0.001	16.9 (1.95-146)	0.01
Cirrhosis	3.2 (1.05-9.81)	0.041	10.8 (1.38-83.9)	0.023
Gastrointestinal malignancy	0.60 (0.22-1.64)	0.322	No outcome	–
Nongastrointestinal malignancy	1.18 (0.70-1.98)	0.545	No outcome	–
Infectious disease	2.71 (1.02-7.26)	0.046	13.0 (3.13-54.5)	<0.001

Mattias Ekstedt et al HEPATOLOGY 2015;61:1547-1554

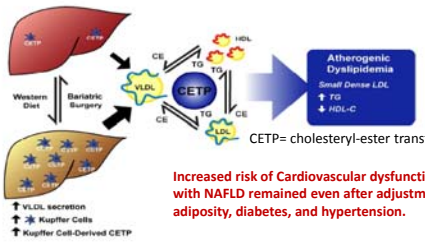
Duration and Degree of obesity matter

- Each year that a young adult is obese raises that person's risk of developing silent heart disease by 2-4%.
- Both overweight (BMI>25) and obesity (BMI >30) duration caused 4% and 7% higher risk of T2D respectively /yr over control non over weight population of women
- Severely obese adolescents (BMI >40) have more advanced liver damage, more severe systemic inflammation
- ALT is a valid test for screening fatty liver, a longer duration of obesity is associated with higher incidence of fatty liver

Jared Reis et al: JAMA. 2013 Jul 17;310(3):280-8. doi: 10.1001/jama.2013.7833.
Hu Y et al: Obesity (Silver Spring). 2014 Oct;22(10):2267-73. doi: 10.1002/oby.20851.
Holterman AX et al: Obesity (Silver Spring). 2013 Mar;21(3):591-7. doi: 10.1002/oby.20174
Tazawa Y et al: Acta Paediatr. 1997;86(3):238

NAFLD- Impact on Cardiovascular issues

A model linking hepatic inflammation and atherogenic dyslipidemia.

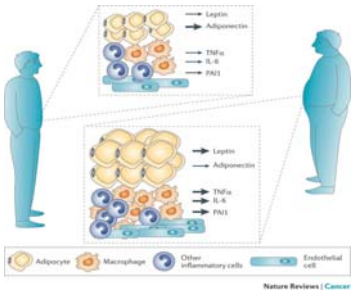


CETP= cholesteryl-ester transfer protein

Increased risk of Cardiovascular dysfunction with NAFLD remained even after adjustment for adiposity, diabetes, and hypertension.

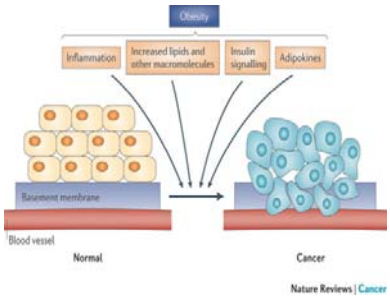
CETP: a Kupffer cell marker linking hepatic inflammation with atherogenic dyslipidemia?
Joel T. Haas, Bart Staels Hepatology August 17, 2015. doi: 10.1002/hep.28125

Changes in adipose tissue in obesity (over several years)



Melin J. Khandekar et. al: Nature Reviews Cancer 11, 886-895 (December 2011)

NAFLD and Cancer



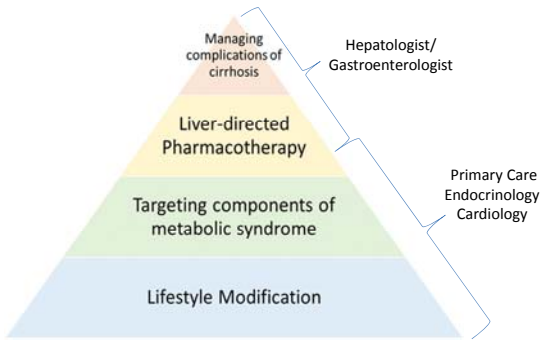
Melin J. Khandekar et. al: Nature Reviews Cancer 11, 886-895 (December 2011)

Extrahepatic cancers in Obesity/NAFLD

Cancer type	Men (95% CI)	Women (95% CI)
Breast	ND	1.12 (1.08–1.16)
Colon	1.24 (1.20–1.28)	1.09 (1.05–1.13)
Endometrial	NA	1.59 (1.50–1.68)
Oesophageal	1.52 (1.33–1.74)	1.51 (1.31–1.74)
Kidney	1.24 (1.15–1.34)	1.34 (1.25–1.43)
Leukaemia	1.08 (1.02–1.14)	1.17 (1.04–1.32)
Melanoma	1.17 (1.05–1.30)	0.96 (0.92–1.01)
Myeloma	1.11 (1.05–1.18)	1.11 (1.07–1.15)
Non-Hodgkin's lymphoma	1.06 (1.03–1.09)	1.07 (1.00–1.14)
Pancreatic	1.07 (0.93–1.23)	1.12 (1.02–1.22)
Prostate	1.03 (1.00–1.07)	NA
Rectal	1.09 (1.06–1.12)	1.02 (1.00–1.05)
Thyroid	1.33 (1.04–1.70)	1.14 (1.06–1.23)

CI, confidence interval; NA, not applicable; ND, not determined. *Relative risks are taken from a meta-analysis of data as reported in Renehan *et al.*[3] and Roberts *et al.*[129]. The relative risk per 5 kg per m^2 increase in body mass index is reported for each site and sex.

Melin J. Khandekar et al: Nature Reviews Cancer 11, 886-895 (December 2011)



Dyson JK, et al. Frontline Gastroenterology 2014;0:1–10. doi:10.1136/flgastro-2013-100404

Weight Management interventions in primary care 2005-2012

Table 2 Patients who received, or did not receive, a weight management intervention over the study period by gender and body mass index (BMI) category

BMI category	Total	Advice	Referral	Drugs	No treatment
Men					
Overweight (BMI 25–29.9)	30 950	1805 (5.8)	913 (2.9)	86 (0.3)	28 282 (91.4)
Obese (BMI 30–34.9)	12 711	1129 (8.9)	762 (6.0)	313 (2.5)	10 697 (84.2)
Severe obesity (BMI 35–39.9)	3368	363 (10.8)	349 (10.4)	333 (9.9)	2499 (74.2)
Morbid obesity (BMI ≥40)	1384	168 (12.1)	239 (17.3)	322 (23.3)	831 (60.0)
Women					
Overweight (BMI 25–29.9)	24 144	1331 (5.5)	762 (3.2)	451 (1.9)	21 794 (90.3)
Obese (BMI 30–34.9)	11 364	925 (8.1)	740 (6.5)	889 (7.8)	9116 (80.2)
Severe obesity (BMI 35–39.9)	4777	462 (9.7)	445 (9.3)	671 (14.0)	3460 (72.4)
Morbid obesity (BMI ≥40)	2715	284 (10.5)	479 (17.6)	724 (26.7)	1578 (58.1)

- **Majority of 91,000 over wt / Obese patients did not get any structured advice or intervention and follow up**
- **Only when BMI >40 was some action taken- but still in a minority**

Booth HP, *et al. BMJ Open* 2015;**5**:e006642. doi:10.1136/bmjopen-2014-006642

Annual Probability of Achieving Normal Weight by Initial BMI Category and Gender: United Kingdom, 2004–2014

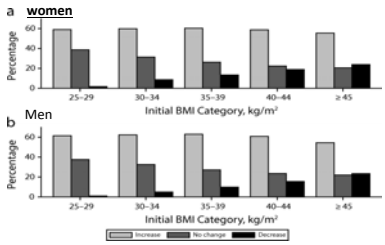
Initial BMI	Total number of Patients	Number of Patient Yrs of follow-up	Number achieving normal BMI	Annual probability of achieving normal BMI Probability (CI)
Men, kg/m^2				
30.0–34.9	27 966	179 746	857	1 in 210 (197, 225)
35.0–39.9	27 490	174 386	249	1 in 701 (619, 797)
40.0–44.9	14 767	91 528	71	1 in 1 290 (1023, 1651)
Women, kg/m^2				
30.0–34.9	27 251	173 066	1 398	1 in 124 (118, 131)
35.0–39.9	27 373	175 356	408	1 in 430 (390, 475)
40.0–44.9	26 716	170 483	252	1 in 677 (599, 769)

BMI = body mass index; CI = confidence interval. Normal weight is having a BMI < 25

Getting back to normal weight is more difficult the heavier you are!

Modified from Alison Fildes et al, American Journal of Public Health: September 2015, Vol. 105, No. 9, pp. e54-e59

What happens after a patient Loses Weight?



Data for subsequent changes in BMI category in participants who showed an initial decrease in BMI category for (a) women and (b) men: United Kingdom, 2004–2014.

Majority of patients who lose weight one year, gain weight the next year!!!

Modified from Alison Fildes et al, American Journal of Public Health: September 2015, Vol. 105, No. 9, pp. e54-e59

Primary care assessment of NAFLD

Suspected NAFLD

- Central obesity, diabetes mellitus, dyslipidemia, metabolic syndrome
- Abnormal LFTs and/or changes on ultrasound consistent with fatty liver

↓

Minimal assessment

- Bilirubin, ALT, AST, GGT, albumin, and fasting serum lipids
- Complete blood count
- Anti-HCV, HB_sAg, ANA
- FBG; if FBG is ≥ 5.6 mmol/L, 75 g OGTT
- Anthropometry: height, weight, BMI, waist circumference
- Blood pressure measurement
- Imaging: abdominal ultrasound

Rule out common causes of abnormal liver tests

Disease or Condition	Test to rule in/rule out
Excessive alcohol use	Corroborative history, CAGE test, GGT/MCV, AST>ALT
Chronic hepatitis B	HBsAg, anti-HBs AB, anti-HBc IgG
Chronic hepatitis C	Hepatitis C antibody reflex to HCV RNA by PCR
Autoimmune hepatitis	Anti-nuclear antibody (ANA) Anti-smooth-muscle antibody (ASMA) Anti-mitochondrial antibody (AMA)
Hemochromatosis	Iron studies-Ferritin/Transferrin Saturation
Thyroid disease	Thyroid function tests (TSH)
Celiac disease	Celiac antibodies (TTG-tissue transglutaminase/EMA)
Medications	Amiodarone, anticonvulsants, methotrexate, tamoxifen, synthetic estrogens,

When should Primary care refer NAFLD patients?

- Another (associated) liver disease suspected
  - Viral or autoimmune serologies are positive
  - Features of Insulin resistance are absent- Normal BMI, younger age, No family history of DM2
- NASH and/or Cirrhosis is suspected

  NASH:
  - Any 3 features Age>50 (obesity >20yrs), T2DM, BMI>35, High transaminases ALT> AST no other cause

  Cirrhosis:
  - Imaging- Nodular liver, splenomegaly, portal htn
  - Labs: AST/ALT ≥1.0, Glob/Alb≥1.0, Platelet count trending down in NAFLD patient
- Treatment with diet/ ineffective or weight loss does not improve liver tests

NAFLD and High Blood Pressure

- Common in patients with obesity/NAFLD/T2DM
- Diet - Low Fructose/carbohydrate, Low sodium
- Medications
  - ACEi /ARB- First line, Neutral or improves IR. Good for heart/kidney/Liver- probably anti-fibrotic
  - Beta-blocker- Worsen IR. Do not use in general. Use vasodilating BB if necessary
  - CCBs- Neutral for IR, better than BB
  - Diuretic- Consider Aldosterone inhibitor +/- Thiazide. Monitor for hyperkalemia when used with ACEi /ARB

NAFLD and Dyslipidemia

- Low HDL, High TG, Variable LDL=Dyslipidemia of IR
- LDL reduction is the only proven strategy
  - Statins are the best. Treat to target if tolerated- LDL 100 for primary prevention in high risk, LDL 70 for secondary.
  - **Indicated in NASH / compensated cirrhosis.**
  - **No increase in liver toxicity in NAFLD over control**
  - **May decrease progression to cirrhosis, decrease HCC**
- Triglyceride-
  - Better glycemic control. If LDL at goal, High TG/Low HDL- okay to consider Fibrate/ High dose Omega-3 as this can convert small dense LDL to fluffier less atherogenic LDL
- HDL?

NAFLD and Type 2 DM

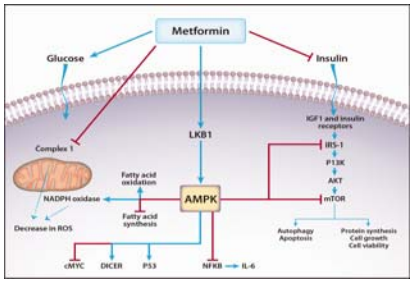
- NAFLD is the Hepatic manifestation of IR and predates DM2(as defined today) by many years to decades
- Until there is Beta cell exhaustion and decreased Beta Cell mass, the blood glucose levels may remain "normal" except with increased carbohydrate load (HbA1C better than FBS)
- Beta cell exhaustion (especially to early phase Insulin secretion after meal) may be reversible with good glycemic control with diet/ Insulin/Oral medications
- "No Insulin → No fatty liver" is still true. Hence while Insulin can/ should be used as needed to bring the blood sugars / HbA1C toward normal, attempts at reducing Insulin resistance and requirement by diet/weight loss/exercise and medications other than insulin should be constantly pursued

NAFLD and Type 2 DM

- **Metformin**
  - Has robust evidence to demonstrate efficacy for glucose lowering in addition to microvascular and macrovascular benefits
  - Acts by suppressing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity via enhancing peripheral glucose uptake, without an increased risk for hypoglycemia.
  - In a multisite analysis in the United Kingdom, about 90% of patients who found metformin IR intolerable due to adverse GI effects were able to tolerate an ER formulation instead
- Patients who continued Metformin after diagnosis of cirrhosis had a significantly longer median survival than those who discontinued it
  - 11.8 vs. 5.6 years overall, P < 0.0001;
  - 11.8 vs. 6.0 years for Child A patients, P = 0.006; and
  - 7.7 vs. 3.5 years for Child B/C patients, P = 0.04, respectively.

Zhang, X., et al, (2014), Hepatology, 60: 2008–2016. doi:10.1002/hep.27199

Rationale for the efficacy of metformin in improving survival in cirrhosis: Pleiotropic effects hypothesis



Modified from Hepatology
Rohit Loomba:Volume 60, Issue 6, pages 1818-1822, 27 OCT 2014 DOI: 10.1002/hep.27314
http://onlinelibrary.wiley.com/doi/10.1002/hep.27314/full#hep27314-fig-0001

NAFLD- Role of Bariatric Surgery-1

- Over 90-95% undergoing Bariatric surgery have NAFLD
- In general, all aspects (fat/inflammation/fibrosis) related to NAFLD are improved with bariatric surgery.
- There are no large prospective controlled studies available, so the issues regarding type of surgery/ amount of weight loss that is optimal has not been determined
- Most studies have excluded patients with cirrhosis
- Decompensation of liver disease post Bariatric surgery have been seriously under-reported (I have personally seen over 10 patients in the last 10 years at URMC)

NAFLD- Role of Bariatric Surgery-2

- Consider Bariatric surgery earlier in those with NAFLD and especially NASH
- In those over 50 yrs (obesity over 20 yrs),those with high risk of NASH/Fibrosis, r/o liver cirrhosis by Imaging, Non-invasive testing +/- Biopsy
- Avoid overaggressive procedures(Biliopancreatic diversion/ long efferent Roux limb). Too rapid weight loss in those with advanced fibrosis (F3/F4) can cause liver failure. Refer such patients only to those surgeons with experience and maturity
- Post OP care critical-a) Micronutrient / essential fatty acid supplementation b) Avoid Alcohol- rapid steatosis/liver failure c) Monitor for increased depression/suicidality

NAFLD Management
Stg 1: Hepatic Steatosis

- All patients with NAFLD should have medical/nutritional counseling, Strategy discussion for weight loss and periodic reassessment and course corrections on a long term basis
- Liver enzymes, Lipid Profile, Glucose HbA1C (Q 6 mth), and US (Q 1-2 yr)can be monitored periodically (Additional testing in those with DM2)
- Patients should a) be screened for cancers more diligently as recommended b) be up to date with vaccinations C) Undergo periodic cardiovascular risk assessment and Rx as needed
- Consider referral to a comprehensive weight loss program, Bariatric surgery if medical management x 2-3 years shows no improvement especially in the age 30-55 years

NAFLD Management
Stg 2: Steatohepatitis

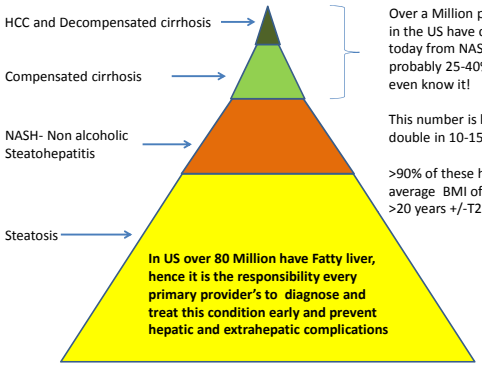
- As in Stage 1- diet/weight loss/screenings
- Would limit alcohol use to as low as possible (< 1 drink/day)
- These patients should be monitored more closely and likely in collaboration with GI/Hepatology
- Periodic blood tests/ Ultrasound based Elastography (non-invasive measures to assess longitudinal progression of fibrosis by GI/Hep) (Future)
- Use of Pioglitazone, Vitamin E , Statins could be discussed though specific guidance is not available in 2015
- Should be offered/considered for clinical trials in NASH
- Early referral for comprehensive weight loss clinic/Bariatric surgery before progression to cirrhosis

NAFLD Management
Stg 3: NASH + Compensated Cirrhosis

- This stage can exceed 10 years in a majority of patients. Patient will need regular visits to PCP + GI/Hep specialist .
- Diet, gradual weight loss / exercise as before
- No protein starvation (1-1.5 gm/kg lean body mass). Exercise to prevent loss of muscle mass
- Continue Statin/Metformin/ACEi or ARB as before. May need to down adjust dose based on hepatic/renal function
- Periodic screening for Esoph Varices/ HCC/ Occult Hepatic encephalopathy
- Q2-3 yr DEXA scans for Bone Density. Ca/Vit D supplements.
- Increased scrutiny for occult cardiac disease/extrahepatic cancers

NAFLD Management
Stg4: Decompensated Cirrhosis

- At this point the focus is on liver failure management and referral for transplant evaluation in the right patient
- Periodicity of reassessment shortened to 1-3 months with CBC/CMP/INR. Monitor for SBP/PNA/UTI/Skin infections
- Most patients will have low BP , GFR and so ACEi/ARB and most other HTN meds should be weaned off to prevent decreased Cardiac output/fluid retention/renal insuff.
- Loop diuretic + Aldosterone antagonist preferred for ascites
- Dose of Metformin/Statin should be decreased/eventually stopped before complications
- Patients with co-morbidities/ age over 70yrs should be guided toward palliative care/hospice in a timely fashion



Over a Million patients in the US have cirrhosis today from NASH and probably 25-40% do not even know it!

This number is likely to double in 10-15 years

>90% of these have an average BMI of >30 for >20 years +/-T2DM

The NAFLD Pyramid

1) R. Loomba, A.J. Sanyal: The global NAFLD epidemic; Nature Reviews Gastroenterology & Hepatology, 10 (2013), pp. 686–690
2) G. Vernon, A. Baranova, Z.M. Younossi: Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults; Alimentary Pharmacology and Therapeutics, 34 (2011), pp. 274–285
3) A.J. Sanyal, N. Chalasani, K.V. Kowdley, *et al*. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis New England Journal of Medicine, 362 (2010), pp. 1675–1685
4) M. Ekstedt, L.E. Franzen, U.L. Mathiesen, *et al.* Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study Journal of Hepatology, 47 (2007), pp. 135–141
5) V.G. Athyros, K. Tziomalos, T.D. Gossios, *et al.* Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet, 376 (2010), pp. 1916–1922
6) Cerasi E. Insulin deficiency and insulin resistance in the pathogenesis of type 2 diabetes: is a divorce possible? *Diabetologia*. 1995;38:992-997.
7) Zhang ZJ, Zheng ZJ, Shi R, Su Q, Jiang Q, Kip KE. Metformin for liver cancer prevention in patients with type 2 diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2012;97(7):2347-2353
8) Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. *Gastroenterology.* 2013;144(2):323-332.